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Early Thoracentesis and Follow-up in Coronary Artery Bypass Graft Patients

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EARLY THORACENTESIS AND FOLLOW-UP IN CORONARY ARTERY BYPASS GRAFT PATIENTS

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Abstract

Coronary artery bypass graft surgery is a high-risk surgical intervention and commonly accounts for hospital readmissions within 30 days of discharge. Pleural effusions that require therapeutic thoracentesis are a reason for many of the readmissions. Studies have examined the adverse clinical effects that large volume pleural effusions have in these patients. However, effusion volume itself may have little influence on patient outcomes. Complications occur without close monitoring and drainage. **In this study, we propose a randomized controlled trial to determine whether frequent follow-up and drainage of pleural effusions ≥320 ml can improve the need for rehospitalization and influence 6-minute walk tests in patients undergoing coronary artery bypass surgery**. We hypothesize that these two interventions will decrease hospital readmission rates and improve 6-minute walk tests in patients within 30 days of hospital discharge. Insights from this study may ultimately help improve the management of coronary artery bypass graft patients.

Chapter 1 – Introduction

1.1 Background

Coronary artery bypass (CABG) surgery, one of the most expensive and often performed surgical procedures, is associated with the need for frequent hospital readmissions[1]. Studies have shown that 12.9%-24% of patients undergoing CABG require hospital readmission and that 80.6% of these occur within 30 days of discharge[2-4]. With the expectation that hospital reimbursements will soon be linked to clinical outcome, the importance of reducing 30-day hospital readmission rates has been emphasized in efforts to lower expenditures[5]. Furthermore, early readmissions following cardiac procedures have been shown to result in more than 3% mortality during hospitalization. With an estimated 600,000 people undergoing CABG surgery in the US each year, a reduction in hospital readmissions in this population would have a profound impact on both hospitals and patients[6].

Many studies have been performed to examine if earlier follow-up after discharge can reduce these hospitalizations. The results have been widely conflicting. While some studies show increased follow-up may lead to a reduction in 30-day readmissions by up to 66% and with it a reduction in hospital cost by 50%[7,8], others demonstrate no benefit[9,10].

In a study of 1,205 CABG patients, 40% of readmitted patients were hospitalized for three days or less, suggesting that many of these cases were preventable[1]. Postoperative pulmonary complications are a leading cause of CABG-associated morbidity[11,12]. Of CABG rehospitalizations within 30 days, up to 23% are due to pleural effusions requiring drainage[1,2,4]. These high readmission rates identify a need for

different management strategies and reveal an unstudied area where a change in practice may lead to improved patient outcomes[13].

1.2 Pleural Effusion Morbidity

Pleural effusions are extremely common in CABG patients, with incidence rates of 40-95% within thirty days following surgery[11,14-17]. Early effusions are usually bloody, caused by trauma from the surgery with bleeding into the pleural space, phrenic nerve injury, disruption of pleural lymphatic drainage by internal mammary artery harvesting, poor chest wall compliance, and diaphragm dysfunction[18]. These effusions range from small, occupying less than one intercostal space, to large, with as many as 10% occupying more than a quarter of the hemithorax. Regardless of size, symptoms may range from asymptomatic to dyspnea, cough, chest pain, and insomnia[16,19]. Many studies have focused on the adverse effects that ensue from larger (>1000ml) effusions, which include atelectasis, arrhythmias, cardiac tamponade, and ventricular diastolic collapse[15,20-22]. Aside from hemodynamic changes, pleural effusions can also affect gas exchange, sleep patterns, walking distance measured by the 6-minute walk test (6MWT), and pulmonary function tests, among others[21,23,24]. These side effects from effusions result in lower recovery rates and increase the need for bed rest, which further puts patients at risk for edema, venous thromboembolism, and pneumonia. Recent literature however has provided evidence that volume of effusion is poorly correlated to clinical impact, suggesting that small volume pleural effusions can be equally hazardous to patient outcomes[15,25].

Patients with pleural effusions undergoing thoracentesis have been documented to yield shorter ICU and hospital stays, which is correlated to lower 30-day readmission

rates[5,20,26]. Although there are no formal guidelines in place regarding the treatment of pleural effusion due to CABG, historical recommendations are that large or symptomatic pleural effusions should be managed with therapeutic thoracentesis at the discretion of the physician[6,15,27-29]. This practice may be called into question since neither the symptoms, such as shortness of breath, nor limitations in physical activity are directly related to volume of effusion[30]. With no data suggesting that small effusions are qualitatively different from clinically detectable ones, recommendations for thoracentesis may be applied to these patients as well.

Ultrasound has been associated with better sensitivity and specificity for diagnosing and quantifying pleural effusions when compared to chest radiograph and does not pose any risk to the patient[20,31,32]. When performed using ultrasound, thoracentesis is widely regarded as a safe procedure[26]. In a study of 9,320 thoracenteses, the overall complication rate was 0.98% with no mortality. Complications included pneumothorax, pulmonary edema, and bleeding episodes, all of which were acutely managed[33]. Thoracenteses may be performed as an outpatient procedure, and are associated with low financial cost aside from the patient and clinician time[15,25]. Therapeutic aspirations for pleural effusions are associated with an immediate improvement in symptoms such as dyspnea and fatigue as well as a return to baseline in 6-minute walk tests, exercise tolerance, total sleep time, expiratory flow, and circulation[14,19,23,24,34,35]. Similar to above, the amount of fluid drained does not correlate with a relief of symptoms or return to baseline. As such, a clear “clinical cut-off volume” recommended for drainage does not exist. However, bedside ultrasound has been used and shown to be reliable in estimating the volume of pleural effusion present.

Thoracentesis was routinely, and safely, performed in one study in whom 500 ml of fluid was thought to be present using the algorithm: Volume = [16 x D] where D represented the distance between the mid-height of the diaphragm and the visceral pleura in end-expiration. In this study, it was suggested that pleural separations below 20mm (320ml effusion size) seen on ultrasound are less clinically significant and more likely to self-resolve[36].

Early diagnosis of pleural effusion may have a significant role in preventing readmissions[1,20]. While two-thirds of pleural effusions occur during initial hospitalization, one-third occurs after discharge and all have a potential to cause complications if left untreated[37]. Standard CABG postoperative protocols involve an exam of the patient one day before surgery, a chest x-ray two days after surgery, and a second exam after 25-30 days[15]. In a prospective evaluation of patients readmitted after cardiac procedures, interventions such as thoracenteses were commonly performed within the first two weeks of hospital discharge, suggesting the need for follow-up within this time period[38].

In a recently published case series, a hospital's cardiothoracic surgery team was alerted to any early post-CABG patient presenting to the emergency department, allowing the team to assess the patient and determine if their condition could be managed without readmission. The high frequency of pleural effusions seen prompted the creation of an outpatient thoracentesis program, which was shown to contribute to a reduction in 30-day readmissions at the hospital[39]. Additionally, a randomized, controlled trial allocated patients to more frequent follow-up within 30 days after CABG discharge and included a lowered, standardized threshold for thoracentesis procedures in pleural effusions. Patients

in the intervention group were examined at days 3-4 and 10-15 and therapeutic aspirations were performed with estimated pleural effusions of 400ml or symptoms of respiratory distress. This group found unrecognized pathology in more than 20% of patients during additional visits and resulted in an increase of 15% in physical recovery rate, as measured by change in patient walking distance. No other controlled studies have examined the effect of thoracentesis on patients after CABG surgery, and the effects on hospital readmissions has yet to be determined[15].

1.3 The role of the Six-Minute Walk Test (6MWT) and modified BORG Dyspnea Scale (mBORG)

The 6MWT has been used to assess how the cardiopulmonary system responds to mild exercise, and it had been found to be an indicator of how well the patient will tolerate daily activities outside the hospital[19]. In addition to measuring the distance a person can walk in 6 minutes, this test also reveals concurrent oxygenation and heart rate. It is often paired with the modified BORG dyspnea scale (mBORG), in which the patient assesses the amount of breathlessness experienced both at rest and during peak levels evoked during the test[19,40]. Associations between 6MWT and treadmill exercise tests have been made, and improvements in distance walked have been correlated with a decrease in cardiovascular events[41]. Early CABG recovery patients tend to be relatively immobile, but mild exercise may elicit symptoms of pleural effusions. In addition to improving symptoms of breathlessness documented by mBORG, thoracentesis for pleural effusions have demonstrated an immediate increase in 6MWT distance[15]. For this reason, many studies assessing the effects of thoracentesis on pleural effusions measure outcomes using both the 6MWT and mBORG.

The goal of the present study is to randomly assign postoperative CABG patients to 1) a more frequent follow-up protocol and 2) a dedicated evaluation and treatment of pleural effusion. The purpose will be to assess the effect of these interventions on 30-day hospital readmissions, as well as to evaluate patient recovery in terms of 6MWT and mBORG. The control population will be assigned to standard postoperative patient follow-up four weeks after hospital discharge. If effusions are present and symptomatic, thoracentesis will then be performed. This group will also be assessed by 6MWT and mBORG. The information from this study may provide insight into lowering hospital readmission rates, thus decreasing hospital cost and patient mortality.

1.4 Statement of Problem

CABG is associated with frequent 30-day hospital readmissions. Within causes for early readmission among post-CABG patients, pleural effusions requiring therapeutic thoracentesis have been cited to be as high as 23%[2]. Despite this, to date there have been no randomized controlled trials among cardiac patients designed to reduce 30-day readmissions due to pleural effusions. Earlier and more frequent follow-up after discharge provides the ability to detect, monitor, and treat these effusions sooner. Furthermore, the excellent safety profile of ultrasound-guided thoracentesis allows providers to manage effusions in an outpatient setting. Together, an intervention consisting of earlier follow-up with concurrent management of pleural effusions may have a significant impact on rehospitalizations in this population. The proposed study provides a low risk, cost effective method geared towards improving patient outcomes.

1.5 Goals and Objectives

With this study, we aim to examine the effect of earlier, more frequent follow-up including screening and protocolled treatment of pleural effusions on reducing 30-day hospital readmissions in patients discharged after CABG surgery. Two secondary aims are to determine if this intervention results in a change in 6MWT distance or mBORG rating, indicators of patient health that have been shown to correlate with hospital readmissions. We plan to examine this through a randomized controlled trial among patients undergoing CABG, a population in which pleural effusions are prevalent but treatment without rehospitalization is largely unstudied. This will provide original insight into the relationship between early management of patients and 30-day readmission in a population at high risk of rehospitalization.

1.6 Hypothesis

We hypothesize that increased follow-up with protocolled thoracentesis for pleural effusions in patients within 30 days of CABG surgery discharge will show a statistically significant decrease in 30-day hospital readmission rates when compared to the standard treatment. We propose that patients in the intervention group will have an improved 6MWT and mBORG at one month compared to those in the control group, in part due to management of pleural effusions.

1.7 Definitions

Protocolled thoracentesis: Ultrasound-guided thoracentesis in patients found to have a pleural effusion larger than or equal to 320ml in size or for effusions causing symptoms, namely dyspnea or chest pain.

Standard follow-up regime: The standard timing and structure of follow-up utilized by the hospital upon discharge of CABG surgery patients.

Six-Minute Walk Test (6MWT): A test designed to measure the distance an individual is able to walk over a total of six minutes on a hard, flat surface.

Modified BORG Scale (mBORG): A scale used to allow individuals to subjectively rate their level of perceived breathlessness both at rest and during exertion.

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Chapter 2 – Review of Literature

2.1 Introduction

An extensive search of the literature was conducted between June 2019 and April 2020 using PubMed, Ovid Medline, Cochrane, and ClinicalTrials.gov electronic databases. In order to identify articles involving pleural effusions found in post-coronary artery bypass graft patients, the following Medical Subject Headings (MeSH) terms were used: “coronary artery bypass graft surgery”, “pleural effusion”, and “thoracentesis” or “follow-up”. Other key search terms included 30-day readmission (early readmission), six-minute walk test (6MWT), BORG (modified BORG, mBORG), CABG (heart surgery, cardiac surgery), and thoracocentesis (fluid removal, drainage). Search criteria was limited to research available in the English language. To date, there are no published guidelines on management of post-CABG pleural effusions, and trials are limited on the subject. To increase the amount of information regarding benign pleural effusions, animal studies were also included in the data set. Abstracts were analyzed to determine article relevancy and those mentioning early or increased follow-up, thoracentesis, or pleural effusion in post-CABG patients were selected. Articles investigating pathology of benign pleural effusions were also included as supplemental material. Throughout the literature search, additional references were identified and obtained from citations in selected papers. Weight was given to randomized clinical trials and systematic reviews, however due to the fact that the topic remains largely unstudied, case series and retrospective observational studies were also included.

2.2 Review of Empirical Studies

The following literature review will aim to analyze current research in three parts. First, data involving the effects of early and frequent follow-up on 30-day readmission rates in post-cardiac surgery and other high-risk patients will be reviewed. Randomized controlled trials investigating different follow-up methods yield conflicting conclusions on early readmission and thus need to be examined in depth. Second, because pleural effusions comprise a large number of potentially avoidable early readmissions in post-CABG patients, the effects of early thoracentesis on outcomes that are associated with 30-day readmissions will be discussed. Finally, data that combines early follow-up with prompt thoracentesis and resultant outcomes will be analyzed. Evidence for early thoracentesis in benign pleural effusions, including post-CABG, is extremely limited and needs to be further examined in large, prospective studies. Given the safety profile of thoracenteses and the identification of subclinical threats pleural effusions pose to the early recovery process in post-CABG patients, there is increasing data to justify the need for the proposed study.

2.2.1 Studies Concerning Earlier and Increased Follow-up on 30-Day Readmission Rates

CABG is associated with a high number of post-operative acute care visits and 30-day readmission rates, and many studies have focused on efforts to improve outcomes. Wong et al. studied the effects that home visits occurring within 7 days of hospital discharge had on 30-day readmission rates in “high risk patients”. Patients who had been hospitalized twice within 28 days (n=332) were randomized upon discharge to early home follow-up or standard outpatient follow-up scheduled within 4-6 weeks. The early home follow-up group received up to four home visits from community nurses within 28

days following discharge, with the first visit occurring by 7 days. The community nurse was able to identify health problems and resolve them or refer the patient back to the hospital for follow-up if necessary. Data was collected at baseline and 30 days after discharge by a researcher blinded to group allocation. The 30-day readmission rate in the study group was 58/166 (34.9%) compared to 62/166 (37.7%) in control, a non-statistically significant (P = 0.648) result. However, the early-visit group experienced improved patient satisfaction with care (P = 0.025)[1].

Limitations of this study are that the authors do not provide detail about timing of or reason for readmission in either group. Furthermore, the interventions able to be performed by visiting nurses were not disclosed, so it is difficult to know the scope of care provided to patients who had already been identified as high risk. Strengths of this study include the assessment of socioeconomic factors as possible confounders and choice of a setting where hospital care was easily accessible to both groups.

Many factors could explain the lack of significance in the primary outcome results. Despite randomization, there were significant differences found between the two patient populations. Patients in the study group were on average older (72.5 years vs. 68.4 years, P <0.001), retirees (89.8% versus 76.5%, P <0.014), receiving social welfare payments (84.3% versus 71.1%, P = 0.006), and had abnormal health assessments (91.6% versus 83.0%, P = 0.020). ANCOVA was performed to account for these differences between baseline variables and no statistically significant difference was found[1]. Notably, patients receiving social welfare did not need to pay for hospitalization, so it is possible that the intervention group had fewer economic barriers to readmission. Additionally, the authors suggest that the use of community nurses rather than advanced practice providers

or specially trained personnel may have limited the level of care available to the study population.

In 2013, Nabagiez et al. recruited cardiothoracic physician assistants to perform home visits. In this randomized controlled trial, the authors evaluated 30-day readmission rates to a single hospital after assigning 701 cardiac surgery patients into physician assistant home care (PAHC) program or the hospital's standard follow-up regimen. Both groups were seen in the office at 2 and 4 weeks after discharge. The control group was seen at home as needed by visiting nurses with no cardiac training. Patients in the PAHC group were visited at home on post-discharge days 2 and 5 by the same PA who treated them before and during their operation. This provided continuity of care to the intervention group and helped the PA choose appropriate care based on the patient's recently observed baseline. The investigators found that 16% (59/361) of the control group was readmitted versus 12% (42/340) in the study group, for a difference in hospital readmission of 25%. The authors documented interventions performed by the PAs and while most were medication adjustments – specifically diuretics – three chest x-rays were also ordered[2]. The results of the x-rays are unknown.

Despite these findings, the study was underpowered and results were found to be insignificant (P = .161). The authors suggest this is not only due to the low number of participants who completed the study, but also due to the low readmission rates in both groups. Notably, both groups were seen within 2 weeks of discharge, half the time that is commonly practiced. The data shows the most significant difference between readmission rates in the two groups during the first two postoperative weeks. Additionally, it shows a large spike in control visits during day 12-15. The early

difference can be attributed to PA visits and recognition of early problems on days 2 and 5 in the intervention group. Whether the spike during days 12-15 could be combatted with another appointment at this time is plausible but unknown.

Dhalla et al. composed one of the largest randomized controlled trials on this subject to study the effects of frequent monitoring via a "virtual ward" on readmission or death in high-risk patients. The control group was discharged with recommendations for outpatient follow-up with their primary care or specialist physician whereas the intervention group was treated by the virtual ward team. The virtual ward consisted of a care coordinator, pharmacist, nurse or nurse practitioner, physician, and clerical assistant. This team was assigned to the patient upon discharge and met daily to design individualized care plans, which they then executed through phone calls, home visits, or clinic visits. Patients were contacted one day after discharge by phone, visited at home by a care coordinator within a few days of discharge, and able to be assessed by any member of the team as needed. On average, patients received 2.8 home visits (SD, 0.95) and were followed by the virtual ward for 35.5 days (SD, 27.0). The 30-day readmission rate in the study group was 18.9% (182/963) versus 21.3% (204/960) in the control group (P = .22)[3].

This study addressed multiple limitations in the randomized controlled trials performed by Wong et al. and Nabagiez et al. Unlike in the study by Wong et al., all 1,932 patients were randomized 1:1 in this trial, and the large sample size helped ensure similar patient characteristics in the groups. Patients in the intervention group were provided with an entire team who were able to increase frequency and duration of follow-up as necessary, which in theory would have been useful given the high level of care provided. By using a team who was not affiliated with the discharging hospital, Dhalla et

al. attempted to create an intervention with generalizability. Unfortunately, this lack of connection with the discharging hospital made communication between providers and patient chart access difficult. This created a limitation in the team's knowledge of what care had and was concurrently being provided to the patient, and may be responsible for the insignificant differences in readmission rates. Continuity of care, a strength highlighted by Nabagiez et al., was also nonexistent in this study as the intervention did not begin until patient discharge[1-3].

With a design that builds upon the strengths of the prior three studies, Hall et al. created the "Follow Your Heart" (FYH) program to measure the effects of early post-operative care by cardiac surgery nurse practitioners on 30-day readmission and death rates in post-CABG patients. The FYH intervention group, which consisted of 169 patients, received two home visits within 7-10 days of discharge by a cardiac surgery NP who had been involved in the patient's hospital care and recovery. The FYH program also consisted of phone calls, 24/7 phone availability by an on-call surgeon, and a routine office visit 10-14 days after discharge. NPs were encouraged to communicate with the patient's providers regularly, which included sending pictures or questions to the cardiac surgeon or moving up appointments if needed. The control group, which consisted of 232 patients, were instructed to return to the cardiac surgical clinic within 2 weeks of discharge for follow-up.

By providing continuity of care and early follow-up with an advanced practice provider specially trained in cardiac surgery, the authors were able to account for some of the limitations previously discussed. After propensity score matching, the control group showed a 30-day readmission rate of 11.54% (18/156) while the intervention group

showed a rate of 3.85% (6/156) (P=0.023), a statistically significant result. In the control group, 3/18 patients were found to be readmitted with pleural effusions, which the authors believe could have been treated with outpatient therapy[4].

Echoing the results of the study by Nabagiez et al., there was also longer interval found between discharge and readmission in the FYH group (18.33 days) than control (8.94 days), highlighting the potential importance of visits beyond the first week of discharge. Unlike in the prior three studies discussed, the experiment by Hall et al. was unable to be randomized due to limitations in NP staffing and schedules. While it is possible selection bias occurred when forming the two groups, propensity score matching compensated for any confounding variables. Ultimately, the results from this study propelled the expansion of the FYH program into three system hospitals.

While we have identified different limitations in each of these studies, there are commonalities that highlight a benefit of increased, more frequent follow-up by specialized providers familiar with patients at high risk for early readmission. Additionally, the studies by Hall et al. and Nabagiez et al. address the ability to treat diagnoses commonly responsible for 30-day readmissions in post-cardiac surgery patients in the outpatient setting, but only Hall's addresses the potential and significant impact of pleural effusions. As pleural effusions are prevalent among this population, further studies should be performed to evaluate the effects that treatment during early visits has on readmission rates.

2.2.2 Studies Concerning Thoracentesis on Patient Outcomes

Many existing studies regarding thoracentesis focus on its impact on physiological functions. In 2007, Spyratos et al. studied the effects of thoracentesis on

expiratory flow limitation (EFL) at rest, a mechanism known to cause dyspnea in patients with chronic obstructive pulmonary disease (COPD). Twenty-one patients with unilateral pleural effusions underwent spirometry and negative expiratory pressure (NEP) testing before and after thoracentesis and a paired t-test was used to compare results. Prior to thoracentesis 14/21 (66.7%) patients were found to be flow limited in supine position. This number decreased to 5/21 (23.8%) of patients after thoracentesis (P = 0.013). Statistically significant differences were also observed in spirometry: forced vital capacity (FVC), forced expiratory volume in one second (FEV1), maximum mid-expiratory flow, and inspiratory capacity all increased after thoracentesis (P <0.004). The mean volume of aspirated fluid was 1,581 ± 585ml, however the authors noted no correlation between volume of aspirated fluid during thoracentesis and improvement in spirometric parameters[5].

A similar small study performed in 2011 by Cartaxo et al. studied the effects thoracentesis had on exercise capacity. Twenty-five patients with unilateral pleural effusions were subjected to spirometry as well as a six-minute walk test (6MWT) before and 48 hours after thoracentesis. By utilizing the 6MWT, the authors were able to assess a patient's capacity to perform a mildly exertional activity rather than only at rest. A statistically significant improvement was found in FVC and FEV1 (P <0.001), echoing the results of Spyratos et al. Additionally, degree of dyspnea measured by mBORG significantly improved at rest (2.7 ±1.3 to 1.5 ±1.4) and during peak 6MWT (5.1 ±2.3 to 2.4 ±1.6) after pleural fluid removal. Walking distance in 6 minutes increased by a mean of 63 meters (14.6%), bringing patients from 73.3% predicted in the presence of pleural effusion to 83.9% predicted after thoracentesis (P <0.001). The authors argued that the

improvement seen is substantial enough to allow a patient to return to their daily activities. Similar to the previous study, although the mean volume of fluid removed was 1,564 ± 695ml, there was no correlation between volume of fluid drained and improvement in either 6MWT or mBORG[6].

In 2012, Marcondes et al. examined the impact of thoracentesis on sleep quality in patients with unilateral pleural effusions. This study consisted of 19 patients with poor sleep quality at baseline, determined by the Pittsburgh Sleep Quality Index (PSQI) questionnaire and full polysomnography (PSG). Patients with dyspnea at rest, a need for supplemental oxygen, or persistent pain were excluded from the study. The group underwent at least two PSGs (six patients completed an additional PSG on the night prior to the first one to account for potential differences from "first night effect"), one on the night prior to drainage and one 48 hours later. The authors saw a statistically significant increase in sleep efficiency (from 76% to 81%, P = 0.006) and decreased percent of light (stage 1) sleep (from 16% to 14%, P = 0.002) following thoracentesis. They also recorded improvements in total sleep time (345 to 407 minutes, P = 0.054) and rapid eye movement (REM), or deep sleep (from 15% to 20%, P = 0.053). The mean volume drained was 1.624L ±796, however authors found no correlation between sleep efficiency and volume of pleural effusion drainage[7].

Limitations of these studies include their small size and lack of randomized controlled nature. Pleural effusions often cause dyspnea at rest and these patients were excluded in the study by Marcondes et al., thus somewhat limiting generalizability. While these case series focus on subclinical symptoms that have been associated with higher readmission rates, the impact on hospitalizations was not studied. Notably, however,

thoracentesis lacked complications or side effects in these studies. Improvements were routinely seen across all three studies; however, outcome measurements were never associated with the volume of pleural fluid. Therefore, these results imply that even small volume thoracentesis may result in improved lung function and sleep, but studies are needed to confirm.

2.2.3 Studies Concerning Earlier and Increased Follow-up with Thoracentesis on Patient and Hospital Outcomes

A clear combination of the two interventions examined in the prior sections comes from a randomized controlled trial performed by Hansen et al. This study addressed the poor 30-day outcomes in post-cardiac surgery patients by assigning 76 patients scheduled to undergo CABG and/or aortic valve replacement surgery to either standard postoperative care or complementary follow-up visits that included clinical exams, focused chest sonography and protocol-driven thoracentesis, if applicable. All patients were seen the day before surgery (baseline) as well as 25-30 days post-operatively, where they were examined and subjected to tests including the 6MWT. Patients assigned to the intervention group were seen for two additional visits: one at day 3-4 and the other at day 10-15 post-op. Thoracentesis was performed in the intervention group if the estimated volume of pleural fluid was 400 ml or more, or if the patient was symptomatic with less fluid. Patients in the control group were subject to the standard regimen, which included thoracentesis only according to physician discretion.

A total of 45 pleural effusions were drained, 22 due to protocol and 23 as a result of x-ray screening or clinical indication. Thus, point-of-care ultrasound improved detection of pleural effusions by 56%. The findings after thoracentesis were similar to

Cartaxo et al., with a mean immediate improvement of 81±42m (22%) found in the 6MWT ($P < 0.0001$). The volume drained was 888±426 ml. Again, there was no correlation found between size of pleural effusion or either symptoms or 6MWT results. At the final visit, patients in the study group were found to have an improvement in physical recovery rate 15% higher than the control group, measured by mean change in walking distance when compared to baseline. Additional pathologies aside from postoperative effusions were discovered and treated in more than 20% of the study group during the two extra visits, which the authors also believed aided in recovery[8].

By introducing a standardized pleural effusion protocol which included the drainage of small, asymptomatic pleural effusions, the authors enrolled patients for thoracentesis who are not regularly intervened on. Although they were unable to validate a clear cut-off volume for intervention, the results indicate that the study group as a whole benefitted from a lower threshold for intervention than is typically performed. With no justification as to why 400ml was chosen as the cut-off for intervention of pleural effusion, we question if thoracentesis on even smaller volumes could further improve outcomes. No individual data was reported, so we cannot evaluate changes in 6MWT based on individual effusion size. The investigators also noted several limitations. First, only 21% of eligible patients enrolled. Second, a double-blind randomized trial was not possible due to the nature of the intervention. Third, it is unknown what happened in the control group regarding pleural effusions. Did some develop and then spontaneously resolve? Finally, patients were not randomized to treatment or observation for ethical reasons.

Hansen et al. addresses the known inverse relationship between decreases in 6MWT and increases in cardiovascular events, recovery time, and rehospitalizations, yet these outcomes were not studied between groups. This study supports the use of thoracentesis on small, asymptomatic effusions discovered at more frequent follow-up appointments; however, a larger randomized controlled trial is necessary. Furthermore, although the intervention was shown to improve 6MWT, a study which correlates this to improved patient outcomes and reduced 30-day readmissions is needed to evoke a change in current management.

2.3 Review of Studies to Identify Confounding Variables

Patients who have previously undergone heart surgery are more likely to have been exposed to patient education and self-care interventions. As a result, these patients may be more likely to have gained additional helpful behaviors through previous hospitalizations which could confound study results[9]. Additionally, increased length of hospital stay, number of bypass grafts, operative time in surgery, and complications during surgery have been found to be associated with higher odds ratio of early readmission[10-12]. These variables have also been correlated with decreased 6MWT distance[13]. Lastly, patients who utilize the hospital system repeatedly are at high risk for subsequent use of services[14]. Even with the proposed intervention, these patients may be more likely to present to the hospital and be readmitted. We will attempt to minimize variables by randomizing study participants and analyzing differences between groups.

Delayed outpatient follow-up has been associated with worse short-term and long-term medication adherence in post-myocardial patients[15]. Although this association has not been studied in our population, most patients are discharged with new medications

after CABG surgery. These medications decrease the likelihood of complications from surgery and improve survival. In order to be enrolled in the study, patients must agree to attend follow-up if randomized to the intervention group. Patients who are more willing to attend follow-up appointments have been shown to have higher rates of medication adherence and are more likely to be invested in their own recovery, which may improve outcomes[16]. This could create a selection bias among participants. Furthermore, if merely having additional appointments scheduled reminds patients to take medication, practice incentive spirometry, and perform rehabilitation exercises, these confounding elements could act to improve 6MWT and reduce early readmissions without the intervention taking place. If these reminders occur at an appointment when patients undergo thoracentesis and the patient subsequently improves, it will be difficult to attribute positive outcomes specifically to thoracentesis. To help reduce potential confounders and further validate study findings, careful documentation of what interventions, if any, are performed at each follow-up visit will be kept.

CABG surgery itself has been shown to increase 6MWT distance[17]. By conducting the 6MWT and mBORG prior to surgery, improvements in both control and study groups are anticipated with retesting on day 25-30. Any improvement in these secondary outcomes noted in the intervention group has the potential to be confounded by the increase in coronary blood flow from CABG surgery and may not be associated with post-operative interventions. We will attempt to control for this with randomization, documentation of surgical factors, and careful comparison between groups.

2.4 Review of Relevant Methodology

This section serves to review literature relevant to the methodology. Please see

Chapter 3 for a more detailed description of the proposed study methods.

2.4.1 Study Design Approach

The proposed study will be a prospective randomized controlled trial (RCT), which is the gold-standard in clinical research. Through this type of study, we will be able to determine if there is a causal relationship between early follow-up with protocolled thoracentesis and 30-day readmission rates. We will control for baseline characteristics between study groups. By incorporating randomization, we will minimize bias and confounding within our sample population.

RCTs are commonly used in studies assessing the effects of early or increased follow-up on patient readmission rates. This design, however, is much less common when assessing thoracenteses on patient outcomes, and most literature consists of case studies. Limitations of these studies include selection and information bias, small sample size, and lack of standards for pleural effusion volume drainage[5-7,18]. The lack of RCTs in this subject is largely due to ethical considerations, where symptomatic pleural effusions cannot be ignored in some patients to determine the effectiveness of thoracentesis. Additionally, previous methods of thoracentesis without ultrasound guidance resulted in a higher rate of complications, making this intervention unlikely to be performed on patients without symptoms[19]. Now that thoracentesis has widely been touted as low-risk, it is feasible to perform a RCT allocating patients to early intervention[8]. This design has been performed by Hansen, et al. and evaluated in the literature review above, and our proposed trial methodology is largely based off this work.

Given the nature of the proposed intervention, neither participants nor providers are able to be blinded. With objective primary and secondary outcomes, there is minimal

risk for bias. Regardless, we will attempt to control for any potential bias by blinding the evaluating researcher, who will assess outcome results without knowing if the patient received the intervention.

Although generalizability may be affected, the proposed trial will be conducted at a single center. The number of patients undergoing CABG surgery annually at Yale New Haven Hospital will be sufficient to show a significant effect and will require less personnel to staff initial and follow-up appointments. By using a single center, follow-up will also be streamlined and documentation will be easily accessible by researchers.

2.4.2 Primary and Secondary Outcomes

An enormous amount of literature has focused on identifying risk factors in order to reduce 30-day readmission rates in patients after CABG surgery. Many studies have noted the high rate of pleural effusions in the readmitted population; however, to date none have evaluated the effects of early pleural effusion management on 30-day readmissions. For this reason, the primary outcome will be 30-day readmission rates in post-CABG patients assigned to early, more frequent follow-up with protocolled pleural effusion treatment compared to participants receiving current standard of care. This will be measured using hospital data as well as by asking all patients about readmission by telephone at 30 days after hospital discharge. Our assessment of 30-day readmission rates defined by hospital records is consistent with prior studies[2,12,20-22], however conducting a brief phone call with the participant will account for any admissions to other hospitals within 30 days of discharge.

One secondary outcome of our study will involve analyzing lung function using 6MWT. Patients in early recovery from CABG surgery are often on restricted activity or

bedrest, and 6MWT has been shown to uncover symptoms of pleural effusion that may go undetected at rest but can hinder recovery[6]. Increases in 6MWT distance have been associated with lower 30-day readmission rates[23]. The studied association between improvements in 6MWT and thoracentesis further link the intervention with our proposed outcomes[6,8].

The mBORG scale is often used concurrently to monitor self-perceived effort at rest and during exercise in cardiac patients[24]. Therefore, it will be administered to patients before and during the 6MWT and values will be compared between groups and evaluated as a secondary outcome. Complication rates following thoracentesis will also be evaluated. Lastly, to support the theory that follow-up visits during the first month do not serve merely to prolong readmission to the hospital, 60-day readmission rates will also be assessed with a brief phone call to each patient.

2.4.3 Study Population and Recruitment Approaches

The selection of the academically distinguished Yale New Haven Hospital (YNHH) for the proposed trial was chosen due to its known high volume of annual CABG procedures. Additionally, YNHH has a CABG 30-day readmission rate of 17.3%, which is comparable to the national rate and high enough to observe a significant difference with our sample size. YNHH has cited their annual rate of CABG procedures to be around 574 patients, which is almost twice that of the sample size needed for our proposed study.

This study will assume that all patients scheduled to undergo CABG surgery who meet inclusion criteria will be enrolled. Patients undergoing emergency CABG procedures have been historically excluded from readmission studies due to the inability

to perform baseline assessments prior to surgery. Our study requires participants to be physically able to perform the 6MWT prior to surgery, therefore patients admitted for emergency CABG or those physically unable to complete the 6MWT prior to surgery will also be excluded from the study. For a more detailed account of the proposed study population, recruitment, and inclusion and exclusion criteria, please see Chapter 3.

2.4.4 Intervention

The traditional practice of conducting the first outpatient visit at 5-6 weeks following CABG hospital discharge is not evidence-based, and continues despite high hospital readmission rates occurring prior to the first appointment[25]. The lack of statistical significance in many studies examining the relationship between earlier patient follow-up and 30-day readmission rates has been repeatedly attributed to the same variables. Components named to be critical to patient rehospitalizations include establishing continuity of care, using appropriately trained providers, and obtaining access to patient information[1-4,21]. By employing trained cardiothoracic providers to perform initial patient assessment in addition to any follow-up appointments, this study ensures that personnel will be capable of addressing and treating post-operative complications. By utilizing the same providers both pre- and post-operatively, a visual baseline will be established, hospital course will be better understood, and appropriate continuity of care will be provided. These providers will be members of the cardiothoracic team handling the patient's surgery, thus any patient information will be easily and instantaneously accessible.

Previous studies have demonstrated the importance of timing of follow-up within the first month. Given the increase in rehospitalizations seen during large gaps between

outpatient appointments, these studies provide evidence for more frequent follow-up in this time period[2,3]. Patient appointments on day 3-4, 10-15, and 25-30 following hospital discharge allow assessment and treatment of immediate and early post-surgical complications. The timing of these appointments also leaves limited time for new symptoms to develop and progress to the point of needing acute hospital care.

The use of ultrasound-guided thoracentesis has been widely accepted as the gold standard treatment for pleural effusions. Other methods of treatment involve higher risks of complications or lack immediate relief in symptoms[19,26]. While studies are in agreement about the procedure protocol, the indication for treatment varies widely between studies and, as a result, no established guidelines exist. Setting a predetermined cut-off volume for pleural effusion intervention provides an easily-followed, standardized approach that will ensure uniform treatment across the study group. Although no correlation was found between volume of pleural effusion and patient outcomes such as respiratory symptoms, sleep, or 6MWT, Usta et al. proposed that volumes lower than 320ml were clinically insignificant, providing a cut-off for our study[27].

2.5 Conclusion

The studies reviewed surrounding the effect of earlier, more frequent follow-up on 30-day readmissions after CABG yields conflicting results with clear limitations. The existing evidence surrounding treatment for post-operative pleural effusions and the effects on various patient outcomes illustrate the potential benefit of early treatment, however they are underpowered and lack randomization. Taken together, these interventions have shown a potential to improve 6MWT in patients, which has been correlated with decreased cardiac events and hospitalizations. The evidence reveals an

unstudied area which has the potential to significantly decrease 30-day readmission rates in post-operative CABG patients, a population at substantial risk. The literature review has highlighted strengths and limitations of each study, which assists in the development of an adequately powered, randomized controlled trial designed to evaluate this two-part intervention on 30-day readmission rates. It also evaluates the methodology used to conduct a standardized study in this patient population with reliable and generalizable results. Lastly, the review aids in the development of secondary outcomes that will help further validate the results and link the study findings to established data.

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Chapter 3 – Study Methods

3.1 Study Design:

The proposed study is a single-center, prospective randomized controlled trial using convenience sampling among hospitalized adults scheduled to undergo elective coronary artery bypass graft surgery. Participants will be recruited and CABG surgery performed on a rolling basis over two years. Prior to beginning the study, an independent researcher will make four sets of 1:1 randomized allocations. The sets will be sealed in consecutively numbered opaque envelopes and patients will be randomized prior to surgery by opening the next sealed envelope.

Patients will be randomized to frequent follow-up including protocolled treatment of pleural effusions (intervention group) or standard postoperative care (control group). Patients will be examined upon admission prior to surgery and a baseline 6MWT with mBORG scale will be administered. Patients in the intervention group will undergo postoperative clinic visits on day 3-4 (visit 1), day 10-15 (visit 2), and day 25-30 (visit 3) following hospital discharge. During these visits, patients will be assessed for pleural effusion using point-of-care ultrasound. Effusions ≥320ml or those causing symptoms will be promptly treated with thoracentesis. The control group will not be seen for a postoperative visit until day 25-30 following the current recommendations and thoracentesis will be performed at the physician's discretion based on the patient's symptoms.

The data for the 30-day hospital readmission rate will be gathered from the hospital's administrative record systems and by members of the study team contacting each study participant to correlate data.

3.2 Study Population and Sampling:

The study will take place from January 2021 until July 2022. Convenience sampling will be used to enroll adults age ≥18 years old referred to undergo elective coronary artery bypass graft surgery at Yale New Haven Hospital. Primary indications for surgery will follow guideline recommendations from the American College of Cardiology (ACC)/American Heart Association (AHA). Inclusion criteria will consist of patients who have a planned CABG surgery, who are able to undergo a 6-minute walk test prior to surgery, and who consent to follow-up with the potential for one or more thoracenteses to be performed over the course of the month following surgery. The need for thoracentesis will be based on the size of the pleural effusion and will be performed if the size criteria is met (320 ml) but the patient appears asymptomatic. The patient must therefore be in a mental capacity to consent and have means for close clinic follow-up, such as transportation and support.

Patients will be contacted and assessed for eligibility by study personnel following identification of qualified patients by clinical providers. The study rationale, risks, and benefits will be explained prior to obtaining written consent. Written consent for any thoracentesis deemed necessary during one-month follow-up period after surgery will be obtained concurrently. Once enrolled, all patients will undergo a 6MWT and evaluate self-perceived dyspnea using the mBORG scale prior to CABG surgery to establish a baseline of functional walking capacity and shortness of breath. All patients will again complete a 6MWT and mBORG scale during their final (day 25-30) visit.

Patients will be excluded if undergoing emergency CABG or requiring concomitant cardiac surgery such as valvular replacement at the time of procedure.

Additional exclusion criteria include patients unable to perform baseline 6-minute walk test, patients being discharged with home hospice, and those simultaneously participating in other clinical trials. Patients will also be excluded from analysis if death occurs during initial admission.

3.3 Subject Protection and Confidentiality:

Prior to patient recruitment, approval for this study will be obtained from the Institutional Review Board (IRB) as part of the Human Research Protection Program at Yale University. Study participants will be given written information regarding the purpose of the trial, expected duration, and benefits and risks of participation, including the risks accompanying thoracentesis. The form will also describe the two treatment groups and randomization process. It will inform the patient of the required intervals for follow-up visits in each group. The patient may withdraw from the trial if at any point they are unsatisfied with treatment or no longer consent to outlined protocol. The patient may also refuse thoracentesis procedure at any time. Written consent will be required on an IRB-approved form prior to enrollment.

Patient information will be kept strictly confidential under regulations of Health Insurance Portability and Accountability Act (HIPAA). Participating researchers will be required to undergo HIPAA training and certification. Electronic patient data collected over the duration of the study will be kept confidential on a server with data encryption software. All data will be deidentified and a randomly generated identification number will be used by researchers to identify participants.

3.4 Recruitment:

Study researchers will screen all hospitalized patients ≥18 years old at Yale New Haven Hospital scheduled to undergo coronary artery bypass graft surgery. Patients meeting eligibility requirements will be approached by recruiters and informed of study guidelines and implications of investigation. Due to time needed to obtain consent and gain baseline functioning with 6-minute walk test, patients admitted for emergency CABG will not be recruited. If the eligible patient is willing to enroll in the study and able to meet follow-up criteria outlined by the study, informed consent will be gathered.

3.5 Study Variables and Measures:

3.5.1 Exposure and Control Variables:

The group subject to intervention will undergo more frequent follow-up with protocolled thoracentesis than the control group. Follow-up visits will occur 3-4 days (visit 1), 10-15 days (visit 2), and 25-30 days (visit 3) after initial hospital discharge. During follow-up visits, patients will undergo point-of-care ultrasound and accompanying thoracentesis if a pleural effusion ≥320ml or symptomatic pleural effusion is found. This will differ from the control group, which will attend only the 25-30 day follow-up and will undergo a thoracentesis at physician discretion.

Additional variables to be obtained include the patients age, gender, race, ethnicity, and prior history of heart failure, renal failure, liver failure, malignancy, hypertension, or obesity. Body mass index (BMI) and pre-/post-operative list of medications will be recorded with anticoagulant use analyzed. A patient's pre-operative INR, hemoglobin and platelet count will be recorded. Heart failure, renal failure, liver failure and malignancy may be associated with the development of pleural effusions. A patient's BMI and use of anticoagulants have historically raised concerns of thoracentesis

complications, although recent studies have suggested safety[1]. Confounding variables are further described later in this manuscript (3.5.4).

Any acute care visit, including to the clinic, emergency department, urgent care setting or other unplanned visit will be recorded as well as the reason for the visit. Special attention will be recorded for dyspnea, pleural effusion presence, congestive heart failure, renal failure, wound infection, and failure to thrive.

3.5.2 Primary Endpoint:

The main outcome for the study is 30-day readmission following discharge after coronary artery bypass graft surgery. Readmission is defined as a readmission to any hospital within 30 days of discharge from index hospitalization. Admissions for rehabilitation, hospital emergency department or urgent care visits, and transfers to and from another hospital are excluded from the definition although they will be recorded.

3.5.3 Secondary Outcomes:

One secondary outcome of the study will be the 6MWT. This will be used as a measure of functional walking capacity and will provide insight into participant's dynamic cardiopulmonary functioning. Patients will have six minutes to walk up and down a measured hard, flat surface (typically, the clinic hallway) as many times as possible. Following American Thoracic Society guidelines, the test will initially be conducted prior to surgery. The test will again be administered in all patients during follow-up day 25-30. During the test, patients will be made aware of each minute that has elapsed, but no encouragement will be given. The 6MWT will be immediately discontinued if patient experiences chest pain, dizziness or other symptoms precluding ongoing testing, with such reasons recorded. Additional secondary outcomes include

complication rates, mBORG scale for self-perceived dyspnea, and 60-day readmission rates.

3.5.4 Confounding Variables:

Potential confounding variables within the study include age, gender, BMI, length of index stay, number of bypass grafts, type of bypass grafts, operative times in surgery, presence of DM, HTN, COPD, history of smoking, number of comorbidities, employment status, number of hospital admissions within the last 365 days, and 5-year average household income. After patient randomization, these characteristics will be assessed for differences between groups.

3.5.5 Point of Care Ultrasound Method:

A low-frequency (3-5 MHz) convex array probe connected to the Sonosite S-ICU ultrasound machine will be used to assess for pleural effusion. Patients will be in supine position with trunk elevation of 15˚. Effusion size will be estimated using the formula (Volume [ml] = 16 x parietal to visceral pleura distance [mm] at the mid-diaphragm). Two independent researchers will view each ultrasound to determine presence of pleural effusion and effusion volume. Symptomatic patients in either group will undergo prompt thoracentesis if pleural effusion is found. Patients allocated to the intervention group will also be subject to thoracentesis if determined to have an effusion ≥320ml, regardless of symptoms.

3.5.6 Thoracentesis Method:

If the patient is consented to undergo thoracentesis, the procedure will be ultrasound-guided and carried out using local anesthesia. A 6-French drainage catheter will be inserted into the pleural cavity and the effusion will be manually drained into a

collection bag, per protocol. The volume of fluid drained will be recorded. Drainage will cease when tap appears dry or the patient is unable to continue drainage due to pain or excessive cough, per clinical protocol. Patients will be observed for 30 minutes following procedure to ensure no complications. Patients will be sent home with information regarding their procedure and instructions to return in the event of worsening dyspnea.

3.6 Blinding of Intervention and Outcome:

Due to the nature of the intervention, it is not feasible to blind patients or providers throughout the study. Patients will be told which group they have been allocated to prior to initial hospital discharge, and will thus either be seen for their first follow-up 3-4 days or 25-30 days after discharge. Providers assessing patients and performing thoracenteses during follow-up appointments (visit 1, 2, and 3) will be unable to be blinded to patient assignment. To control for information bias, primary and secondary outcome assessment will be performed by a researcher blinded to group allocation.

3.7 Assignment of Intervention:

Participants who meet inclusion criteria will be randomly allocated to either the intervention or control group in a matched 1:1 ratio following randomization protocol outlined above. Prior to obtaining consent, patients will be informed of both group assignments and will agree to participate in the study regardless of group allocation. As mentioned, neither patient nor researcher conducting follow-up visits can be blinded to the intervention, however researchers analyzing outcome data will be blinded. Further attempt will be made to match confounding variables in both the control and intervention group.

3.8 Adherence:

All study participants will be evaluated 25-30 days following index hospitalization discharge to assess for adherence to follow-up protocol. Documentation from each follow-up visit including ultrasound findings and procedure codes will be accessed for patient and physician adherence. If patients assigned to the intervention group do not present to either visit 1 or 2, this will be documented. To prevent participant dropout due to missed appointments, members of the research team will contact participants via telephone two days prior to each appointment. Attempts to reschedule patients within the follow-up appointment windows will be made if participants are unable to attend scheduled appointments. If at any point patients refuse recommended thoracentesis, this will also be documented.

3.9 Monitoring of adverse events:

Following thoracentesis, patients will be monitored for 30 minutes for adverse effects. A chest x-ray will be obtained if there is any concern about complications that occurred as a result of the procedure. In this trial, adverse effects will include pneumothorax, bleeding, or infection after thoracentesis. Patients will be discharged home with information regarding pleural effusions and warning signs that should prompt the patient to contact their provider. Any complication arising during follow-up visits that results in rehospitalization, patient disability, or requiring intervention to prevent permanent patient impairment will be documented and reported.

3.10 Data collection:

Patients referred for CABG who have met study eligibility criteria will meet with researchers to obtain initial 6-minute walk test and dyspnea data and undergo

randomization into either control or intervention group. Patient data including age, gender, BMI, presence of DM, HTN, COPD, history of smoking, number of comorbidities, and 5-year average household income will be gathered. During the operation, number of bypass grafts, type of bypass grafts, and operative time will be recorded by a researcher. Prior to discharge, group allocation will be discussed with patient and follow-up visits will be scheduled and recorded.

Data in the form of readmissions to Yale New Haven Hospital will be collected for 30 days following a patient's initial discharge. During the 25-30 day follow-up visit, patients will again undergo a 6MWT with mBORG rating and data will be recorded by a researcher blinded to patient allocation. A researcher will contact patients by phone at day 30 and day 60 to inquire about any hospitalizations since CABG discharge.

3.11 Sample size calculation:

The incidence of 30-day readmission in CABG patients is cited to be 16.5%[2]. The proposed study assumes an absolute difference in incidence of 30-day readmission rate of 66%, as shown in other studies of 30-day readmission rates among the same patient population[2]. Utilizing Power and Precision statistical software, a difference of proportion calculation was performed assuming a 2-tailed hypothesis, alpha of 0.05, and power of 80%, yielding a sample size of 126 patients per group. A minimum of 252 patients would be required for enrollment, however the final sample size will also account of an estimated 20% dropout rate as evidenced by other literature. Thus, a total of 303 patients will be enrolled in the study to detect a significant effect.

3.12 Analysis:

Descriptive variables will include confounding variables previously mentioned (3.5.4). Student's T-test will be utilized for comparison of continuous variables, which will be reported as a mean (standard deviation) or median (interquartile range). Chi-square testing will be used for comparison of categorical variables, which will be reported as frequencies. Readmissions at 30 days will be reported as a frequency. Baseline patient characteristics will be collected and recorded during the initial pre-surgical visit. Hospital course and CABG procedure characteristics including length of index stay, number of bypass grafts, type of bypass grafts, and operative times in surgery will be obtained during post-op day 25-30 visit. All statistical tests will be two-tailed, and deemed significant if P-value ≤ 0.05 is reported. Intention-to-treat analysis will be used. Data will be evaluated using Statistical Analysis software. After randomizing and matching patient characteristics to account for confounders, univariate models will be used to analyze the outcome of interest. If significant discrepancies are found between groups, we will use multivariate analysis.

3.13 Timeline and Resources:

This study will be performed over a two year time period. Enrollment and hospital index will occur over an 18 month period, beginning January 2021. Data collection will continue for 30 days following discharge of the final patient enrolled. The last follow-up visit will be completed by August 2022, reserving the final four months for statistical analysis. Each patient enrolled will be analyzed independently by research assistants on a continuous basis depending on date of hospital index. The proposed research study will require two cardiothoracic providers trained in ultrasound-guided pleural effusion diagnosis and management. These providers will be dedicated to recruiting patients,

performing pre-operative evaluation, and conducting post-operative outpatient visits. An additional two personnel will be needed to schedule patients for follow-up appointments and send phone call reminders, perform chart review, assess for primary and secondary outcomes, and call patients at post-hospital discharge day 30 and 60. A final two personnel blinded to the study allocation will be utilized to evaluate results.

3.12 References

1. Puchalski JT, Argento AC, Murphy TE, Araujo KLB, Pisani MA. The Safety of Thoracentesis in Patients with Uncorrected Bleeding Risk. 2013;10(4):336-341.
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Chapter 4 – Conclusion

4.1 Study Advantages and Disadvantages

The major strengths of this study lie in its novel clinical design. Evaluations of 30-day CABG readmissions have cited pleural effusions requiring thoracentesis as a major cause, however no studies to date have examined the effect drainage has on this outcome. Past studies exploring thoracentesis on other outcomes have lacked significant sample size, randomization, and control groups. These studies have also failed to identify a clinical cut-off volume for which thoracentesis is no longer beneficial.

The proposed study is the first randomized controlled trial to evaluate increased follow-up with protocolled pleural effusion management on 30-day readmission rates in CABG patients. By randomizing participants, we will decrease potential selection bias and strengthen generalizability of results. The use of a protocolled plan which includes volume of pleural effusion warranting thoracentesis will provide consistent, objective data free of operator variables.

Earlier outpatient follow-up in CABG patients will allow closer monitoring and treatment of adverse effects not strictly limited to pleural effusions. This could potentially avoid more serious complications or lead to earlier treatment if the patient still requires hospitalization. By establishing contact with the patient prior to CABG, the examiner will have a baseline assessment and be able to provide meaningful continuity of care. This study also proposes a low-risk, ethical intervention. The simplicity of bedside ultrasound combined with outpatient appointments ensures a low-cost practice that can be widely implemented if found to significantly improve outcomes.

With the nature of the intervention comes potential limitations. Patients and investigators are unable to be blinded in this study. Due to ethical concerns, any adverse outcome that is able to be intervened upon during outpatient visits will be addressed, potentially lowering hospital readmission rates regardless of pleural effusion presence. Additionally, it would be unethical to monitor symptomatic pleural effusions without intervention. These interventions will be rigorously reported.

In order to obtain baseline 6MWT and mBORG data from patients in both groups, these variables will be measured during the initial enrollment meeting prior to CABG surgery. Follow-up data collection will occur during day 25-30, when the control group is first seen after hospital discharge. Due to timing of initial evaluation, any improvements seen in these secondary outcomes may exist due to increased coronary blood flow from CABG surgery, independent of the proposed intervention.

The study may be affected by large drop-out rates. Brooke et al. found that older patients were less likely to attend outpatient follow-up appointments if they believed the appointments would not add value[1]. This has the potential to remove patients from the study who are recovering without complication and would thus contribute to lower readmission rates in the intervention group. Additionally, asymptomatic patients in the intervention group with effusions ≥320ml may not consent to a thoracentesis procedure, which would result in their removal from the study.

Despite significant attention given to patient population and resources, there are still aspects of the study that limit generalizability. First, the study will be conducted at a single center. Second, thoracentesis will be performed by a trained provider who has been involved in the patient's cardiothoracic care. Low complication rates have been reported

when experienced operators are utilized, however this may not always be available outside of the study institution.

4.2 Clinical and Public Health Significance

30-day readmission rates after CABG surgery are extremely high. These readmissions are also extremely costly to the hospital system and at risk of no longer being reimbursable by insurance companies. This has prompted numerous trials designed to reduce rehospitalizations, however conflicting evidence and lack of prospective nature have yielded no change in practice. Unfortunately, while patients undergo CABG with the goal of improving their health, pleural effusions are a common complication from surgery that often bring patients back into the hospital. With readmission, patient mortality rate increases, recovery rate slows, and patients are put at higher risk for infection[2].

If successful, this study would provide evidence to suggest a change in the way providers follow-up on hundreds of thousands of patients every year. The introduction of earlier follow-up with a provider who has seen the patient prior to surgery will also provide continuity of care and allow any concerns or early symptoms to be addressed and treated. The results of this study may also help establish guidelines for the treatment of benign pleural effusions, which to date is subject to significant variability due to its dependence on clinician discretion. Outpatient ultrasound screening and treatment for pleural effusion is a low-cost procedure that has the potential to save a hospital millions of dollars per year. Further studies to identify whether even smaller volume pleural effusions benefit from drainage may be warranted. The proposed intervention of this

study may be effective in reducing 30-day CABG readmissions and with it patient morbidity and mortality.

4.3 References

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2. Weissman C. Pulmonary complications after cardiac surgery. *Seminars in cardiothoracic and vascular anesthesia.* 2004;8(3):185-211.

APPENDIX A: Sample Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR.1

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: *EARLY THORACENTESIS AND FOLLOW-UP IN CORONARY ARTERY BYPASS GRAFT PATIENTS*
Principal Investigator: *Jonathan Puchalski, MD, Med and Jessica Kohler, PA-SII*
Funding Source: *Yale School of Medicine*

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to investigate the relationship between early outpatient follow-up paired with protocolled thoracentesis and the possible decrease of 30-day hospital readmissions. You are being asked to participate because you are at least 18 years of age and are scheduled to undergo elective coronary artery bypass graft (CABG) surgery. Approximately 300 individuals will be participating in this study.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will also discuss with you. This discussion should take place over all aspects of this research study—its purpose, procedures that will be performed, any potential risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate. If you agree, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, no change will occur to your planned CABG procedure or subsequent hospital stay. During today's visit, we will ask you to perform one 6-minute walk test. For this, you will be asked to walk as far as you can in six minutes with the distance and your oxygen saturations being recorded. We will also ask you to determine how short of breath you are using a scale from 0-10. These are tests that are not performed for people who do not consent to participating in the study.

All patients will have a follow-up appointment 25-30 days after discharge from the hospital. You will be randomly assigned to receive either (a) additional outpatient follow-up on day 3-4 and day 10-15 following hospital discharge with accompanying treatment for any pleural effusions found to be symptomatic or ≥320ml in size, OR (b) standard outpatient follow-up on day 25-30. During your follow-up appointment on day 25-30, all patients enrolled will again undergo a 6-minute walk test and fill out the modified Borg scale.

If you are randomized to the additional follow-up group (a), you will attend three outpatient appointments (on day 3-4, day 10-15, and day 25-30 post-discharge) where you will be evaluated by a cardiothoracic surgery provider. During the appointment, your provider will assess for any pleural effusions using a handheld ultrasound probe. If

pleural effusions are present, your provider will determine the size and assess you for symptoms. Any effusion found to be causing symptoms or ≥320 ml during these visits will be promptly drained using thoracentesis method, described below. During your visit, your provider will ask about your recovery and any additional symptoms you may be experiencing. They may adjust your medications if necessary.

If you are randomized to standard follow-up group (b), you will only attend the standard outpatient appointment 25-30 days after hospital discharge. During this appointment, your provider will ask about your recovery and any additional symptoms you may be experiencing. If you are having symptoms including difficulty breathing, shortness of breath, or dry cough, your provider may assess for a pleural effusion using a handheld ultrasound probe. An effusion found to be responsible for symptoms will be drained using thoracentesis if your provider deems it to be necessary. During this visit, your provider may also adjust medications if necessary.

Both groups (a) and (b) will undergo another 6-minute walk test and rate self-perceived dyspnea during the standard outpatient follow-up appointment 25-30 days after hospital discharge. During this visit, you will be asked if you have been readmitted to the hospital at any time during the month. You will also receive a follow-up phone call at day 60 asking if you had an unplanned visit or admission to the hospital during this time and if so, the reason for readmission.

In this study, you will be asked to adhere to your assigned medication regimen and recovery exercises at the prescribed frequency and dosage. The total amount of time of enrollment in this study would be 1 month following your CABG hospital discharge, with one additional phone call at 2 months.

A description of this study will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. The purpose of this database is to allow everyone to see information on what studies are being done, and what studies have already been done. At most, the website will include a summary of the results. You can search this website at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate. Research results will not be returned to your clinician. If research results are published, your name and other personal information will not be disclosed or given.

Thoracentesis Procedure

This procedure removes fluid that has built up in the space between the lungs and ribs (called a pleural effusion). During this procedure, the area where the needle goes is numbed by an injection of a local anesthetic. The needle then goes through the skin, between the ribs and into the fluid around the lung. A catheter is advanced over the needle and the fluid is removed. At the end of the procedure, the catheter is taken out. A dressing is put over the area. If you have new symptoms following the procedure, a chest x-ray may then be taken.

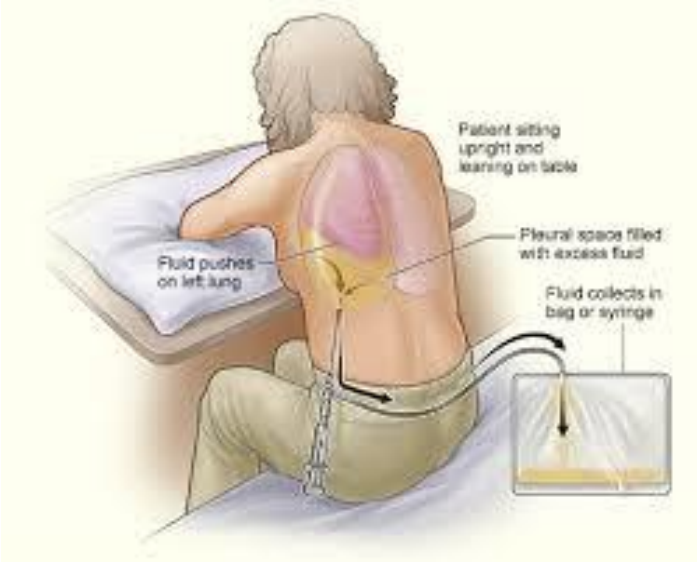

Fig 1. National Heart, Lung, and Blood Institute

Risks and Inconveniences

In recommending this procedure, your provider has balanced the benefits and risks of the procedure against the benefits and risks of not proceeding. Your provider believes there is a net benefit to the procedure. Symptoms during and after the procedure are uncommon, but include shortness of breath, coughing, fainting, or pain. Rare risks and complications include bleeding into the space between the lungs and ribs, the build-up of air or fluid into the lung, damage from the needle to nearby parts of the body (i.e. liver or spleen), collapsed lung which may require chest tube insertion to reinflate the lung, wound infection, thrombosis, or in extremely rare cases, death. The overall risk of complications from a thoracentesis is less than 1%.

Other risks from participating in the study include the breach of confidentiality about your health status and participation in the study. This is unlikely to happen, as all study investigators are trained and certified in research privacy, as well as HIPAA.

Benefits

The potential benefit resulting from the study is a decrease in the chance of being readmitted to the hospital after CABG surgery, especially during the first 30 days after discharge when readmissions are common. Other benefits include closer follow-up with your cardiothoracic provider, where you will be able to have any symptoms or concerns addressed and treated promptly. By undergoing immediate treatment of pleural effusions found during your outpatient visits, you may be less likely to suffer from discomfort or symptoms which slow your post-surgical recovery.

This study may also provide better insights to treatment guidelines for patients undergoing CABG surgery, which may lead to faster, improved recovery and better outcomes.

Economic Considerations

No compensation will be made to subjects enrolled in this study. You will still be responsible for any co-pays required by your insurance company for standard treatment.

There are no other costs associated with your participation in the study. Parking at your follow-up appointments will be provided free of charge.

Treatment Alternatives/Alternatives

If you choose not to participate in this study, you will receive the current standard follow-up at Yale New Haven Hospital. This means you will schedule a follow-up appointment with your provider 25-30 days following hospital discharge to assess how you are recovering.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child, abuse of an elderly person, or certain reportable diseases. Information will be kept confidential by using only identification numbers on study forms, storing signs forms in locked cabinets, and password protecting data to be stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

We understand that information about your health is personal and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies your personal health information. This may include information that might directly identify you, such as name, address, telephone number, email address, and/or mobile phone number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you and your coded information. This link will be kept secure and available only to the principal investigator, or selected members of the research team. Any information that can identify you will remain confidential. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for five years. After five years, the link will be destroyed, and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- Research study records
- Records about phone calls made as part of this research
- Records about your study visits

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who many need it for research purposes.

All healthcare providers subject to the Health Insurance Portability and Accountability Act (HIPAA) are required to protect the privacy of your information. The

research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of you or your child's information.

If you choose to participate in this study, the investigators will check your electronic medical record at Yale via EPIC to make sure you qualify. Any access to your electronic medical record will be done consistent with HIPAA regulations.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Your healthcare outside the study will not be affected if you do not agree to participate. However, you will not be able to partake in this research study and will not receive study procedures as a participant if you do not allow use of your information as part of this study. You do not give up any of your legal rights by signing this form.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research time at any time and tell him or her that you no longer wish to participate. This will cancel any future appointments.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

The researchers may withdraw you from participating in the research, if necessary. This will only occur if you do not adhere to the assigned treatment.

If you choose not to participate, or if you withdraw, it will not harm your relationship with your treatment team or with the Yale New Haven Hospital.

Questions

We have used technical and/or legal terms in this form. Please feel free to ask about anything you do not understand and to consider this research and the permission form carefully—as long as you feel necessary—before you make a decision.

Authorization

I have read, or someone has read to me, this form and have decided to participate in the project described above. Its general purpose, the specifics of my involvement, possible hazards, and possible inconveniences have been explained to my satisfaction. My provider has also explained the thoracentesis procedure and I understand the risks, including the risks that are specific to me. I understand that no guarantee has been made that the procedure will improve my condition. I understand that I have a right to change my mind at any time, including after I have signed this form, but preferable following a discussion with my provider. My signature indicates that I have received a copy of this consent form.

Name of Subject: _____
Signature: _____
Relationship: _____
Date: _____

_____ _____
Signature of Person Obtaining Consent Date

If you have any further questions about this project, or if you have a research-related problem, you may contact the Principal Investigator, Dr. Jonathan Puchalski, or co-investigator Jessica Kohler, PA-SII.

If, after signing this form, you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk to someone other than the researchers to discuss problems, concerns, and/or questions you may have regarding the research, or to discuss your rights as a research subject, you may contact the Yale Human Investigator Committee at 203-785-4688.

APPENDIX B: mBORG Scale of Perceived Exertion

Instructions:

This scale is used to determine if you feel short of breath at rest and with exercise.

Using the scale below, please rate your level of breathlessness from 0, meaning no shortness of breath, to 10, meaning maximal breathlessness.

Scoring	Description	Shortness of Breath at Rest	Shortness of Breath with Exertion
0	No breathlessness at all	☐	☐
0.5	Very, very slight (just noticeable)	☐	☐
1	Very slight	☐	☐
2	Slight breathlessness	☐	☐
3	Moderate	☐	☐
4	Somewhat severe	☐	☐
5	Severe breathlessness	☐	☐
6		☐	☐
7	Very severe breathlessness	☐	☐
8		☐	☐
9	Very, very severe (almost maximal)	☐	☐
10	Maximal	☐	☐

APPENDIX C: Sample Size Calculation

Calculated using Power and Precision 4 Software

Alpha	0.050
Tails	2
Power	80%
Control Proportion Positive	0.165
Intervention Proportion Positive	0.055
Rate Difference	0.11
N Per Group	126
Number of Groups	2
Total Required Participants	252
Standard Error	0.039
95% Lower	0.034
95% Upper	0.186

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